986 LOCAL AND LYMPHOID IMMUNE SURVEILLANCE MECHANISMS IN "EXCEPTIONAL SURVIVORS" OF STAGE IV BREAST CANCERS FOLLOWING STANDARD OF CARE CHEMO- AND TARGETED THERAPIES

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Background Breast cancer patients with metastatic disease can exhibit rapid disease progression, disease stabilisation or partial responses of varying duration. However, for reasons that are not fully elucidated, a small fraction of patients will elicit an exceptional durable response to standard anti-cancer treatments or survive significantly longer than patients with clinically comparable tumours. Here, we investigate the drivers of immune surveillance mechanisms of long-term survivors of metastatic breast cancers.

Methods Peripheral blood mononuclear cells (PBMCs) from long-terms survivors of metastatic breast cancer patients alongside matched control cohorts of stage IV rapid progressors and typical responders, early breast cancer patients and healthy volunteers were isolated. High-dimensional flow cytometry and proteomic analysis of the PBMCs across these groups was performed. In vitro activation of candidate immune cell types isolated from PBMCs was conducted for downstream proteomics analysis of activated phenotypes.

Results Principle Components Analysis (PCA) showed distinct segregation of the exceptional survivors from the other control groups with an immune signature in exceptional survivors constituting of activated NK, CD8 T cells and gd T cells pointing towards higher innate immunogenicity in these individuals. Specifically, although these metastatic exceptional responder patients possessed comparable NK cell frequencies, the proportion of $NKG2D^{+}CD56^{dim}CD16^{+}$ NK cells were significantly enriched compared to the typical responders. Additionally, proportions of $CD8^{+}$ central memory ($CD45RA^{-}$ $CD27^{+}$) and effector memory ($CD45RA^{-}$ $CD27^{-}$) Vd1 and Vd2 gd T cells, were also seen to be significantly increased. Moreover, proteomics analysis on PBMCs of the responders revealed proteins involved in cell cycle progression and cell proliferation such as RBBP7, KCTD10 and PTH2 were elevated in the exceptional responders compared to the typical responders. Functional in vitro validation of these findings by analysing the proteome of activated immune effector cells along with scRNA sequencing of lymph node and tumour tissue is currently underway.

Conclusions To our knowledge, this work is the first to explore in depth the immune signatures in the peripheral blood of exceptional survivors with metastatic breast cancer. Elucidating the immunological reasons for favourable atypical responses alongside functional tumour microenvironment analysis offers unique insights for predictive biomarker identification and discovery of axes that could be exploited therapeutically to benefit those with less favourable responses.

Ethics Approval Written informed consent was obtained from all individuals in accordance with the Declaration of Helsinki under the following research ethics committee; London-Chelsea approved study (REC ID 13/LO/1248).

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